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International Classification:—**A61k. C07c.**

COMPLETE SPECIFICATION

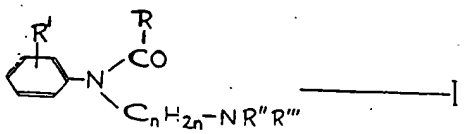
N-Substituted Anilides and their preparation

We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of new N-substituted anilides having analgesic properties.

In the past, numerous substituted ethylene diamines have been prepared. For example, *Chemical Abstracts 43,* 593C, describes N-(3-diethylaminopropyl)-formanilide. This compound and closely related compounds described in the prior art are inactive as analgesics when tested as hereinafter described.

The new N-substituted anilides of the present invention which are in general active as analgesics, have the general formula:

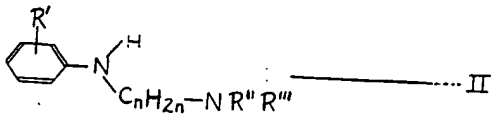


I

in which R is an alkyl group containing 1 to 4 carbon atoms, R^1 is hydrogen, halogen, dihalogen, hydroxyl or an alkyl, alkoxy, alkanoyloxy, or an alkanoylamino radical containing not more than six carbon atoms, R^{11} and R^{111} are alkyl radicals, each containing not more than six carbon atoms, or when taken together with the nitrogen atom to which they are attached form the residue of a saturated heterocyclic amine, and n is 2 or 3.

These new N-substituted anilides of the present invention are, in general, liquids at room temperature, which are relatively insoluble in water but soluble in most organic solvents. They form salts with mineral acids which are soluble in water and alcohol but relatively insoluble in ether. The acid addition salts are generally crystalline solids, as shown in the examples hereinafter.

In accordance with the invention these new N-substituted anilides having the general formula I are prepared by reacting an N-substituted aniline having the formula:



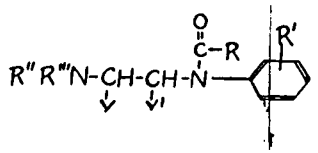
II

in which R^1, R^{11}, and R^{111}, and n are as defined above, with an acylating agent containing the group RCO, in which R is as defined above.

When the acylating agent is a liquid, the reaction can be carried out by heating with the N-substituted aniline of formula II. The reaction can be carried out, for example, by heating on a steam bath for 1 to 6 hours. The acylating agent may be an acyl anhydride or an acyl halide.

The following tables summarize the compounds of the present invention prepared by the examples described hereinafter.

TABLE I



$R^{II}R^{III}N$	R^1	Y	Y^1	R	B.P. °C.	Mono HCl m.p. °C.	Procedure of Example
Dimethylamino	H	H	H	ethyl	115—118/1.8	138—141	1
"	H	H	H	propyl	110—115/0.3	132—133	4
"	H	H	methyl	ethyl	117—122/0.2		1
"	*p*-methyl	H	H	ethyl	118—123/0.6	144—145	1
"	*p*-methyl	H	H	*iso*propyl	112—115/0.1	179—180	5
"	*p*-ethyl	H	methyl	ethyl	120—124/0.2	184—185	1
"	*m*-chloro	H	H	ethyl	142—144/2.5	125—127	1
"	*m*-chloro	H	methyl	ethyl	120—122/0.7	146—148	1
"	*m*-chloro	H	methyl	propyl	125—127/0.7	183—184	4
"	*m*-hydroxy	H	methyl	ethyl	170—190/0.8		3
"	*m*-hydroxy	H	methyl	propyl	180—190/0.8		3
"	*m*-propionyloxy	H	methyl	ethyl	150—154/0.8		1
"	*p*-propionamido	H	H	ethyl	215—220/0.2	169—172	1
Diethylamino	H	H	H	ethyl	130—133/1.5		1
"	H	H	H	propyl	135—137/1.8		4
"	H	H	H	*iso*propyl	105—110/0.8		5

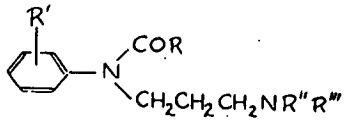
TABLE I (Cont.)

$R^{11}R^{111}N$	R^1	Y	Y^1	R	B.P. °C.	Mono HCl m.p. °C.	Procedure of Example
Diethylamino	H	H	H	butyl	142—146/1.5		1 and 6
"	*o*-methyl	H	H	ethyl	116—120/0.2		1
"	*m*-chloro	H	H	ethyl	140—144/0.9		1
"	*m*-chloro	H	H	butyl	148—152/0.5		1 and 6
"	*p*-chloro	H	H	ethyl	140—142/0.5		1
"	2,4-dichloro	H	H	ethyl	138—144/0.2—0.5		1
"	*m*-bromo	H	H	ethyl	138—142/0.3		1
"	*m*-methoxy	H	H	ethyl	152—156/1.0		1
"	*m*-methoxy	H	H	propyl	148—151/0.8	82—84	4
"	*p*-ethoxy	H	H	ethyl	144—148/0.3		1
"	*m*-propionyloxy	H	H	ethyl	146—152/0.3		1
Dibutylamino	H	H	H	ethyl	132—134/0.3		1
"	H	methyl	H	ethyl	150—154/0.7		1
"	*m*-chloro	H	H	ethyl	140—144/0.3		1

TABLE I (Cont.)

$R^{II}R^{III}N$	R^1	Y	Y^1	R	B.P. °C.	Mono HCl m.p. °C.	Procedure of Example
Piperidino	H	H	H	ethyl	150—152/1.0	125—127	1
„	H	methyl	H	ethyl	128—134/0.8		1
„	H	methyl	H	propyl	148—152/0.5		4
„	H	H	methyl	ethyl	142—152/2.3	201—202	1
„	H	H	methyl	propyl	134—138/0.2		4
„	H	H	methyl	*iso*propyl	144—150/0.3		5
„	H	H	methyl	butyl	138—144/0.2		1 and 6
„	*m*-chloro	H	H	ethyl	148—152/0.5		1
Pyrrolidino	H	H	H	ethyl	132—136/0.5	128—130	1
„	*m*-chloro	H	H	ethyl	146—150/0.7	129—131	1
Morpholino	H	H	H	ethyl	154—160/0.8		1
„	H	methyl	H	ethyl	146—150/0.3	156—158	1
„	H	H	methyl	ethyl	144—148/0.7	189—190	1
„	*m*-chloro	H	H	ethyl	154—160/0.2	189—191	1

TABLE II



$NR^{II}R^{III}$	R^{I}	R	B.P. °C.	Mono HCl m.p. °C.	Procedure of Example
Dimethylamino	H	C_2H_5	121—124/0.6	170—172	1
„	H	C_3H_7	117—122/0.1	160—161	1
„	*m*-chloro	C_2H_5	130—134/0.2		1
Diethylamino	H	C_2H_5	145—150/2	153—154	1

The N-substituted anilides of the present invention are active analgesics when measured by the mouse hot plate method described by Wolfe and McDonald (*J. Pharmacol. Exptl. Therap.* 80, 300—307) with modifications. The compounds are suspended in 2% aqueous starch and administered subcutaneously to a group of three mice at a dosage of 50 mg./kg. These mice are then individually placed upon the top enclosed surface of a copper bath maintained at 59° ± 0.5° C. by a boiling acetone-ethyl acetate mixture. The response to this presumably painful heat stimulus is either a licking of the paws or an attempt to jump from the plate. The response time is measured four times for each mouse at fifteen minute intervals following administration. The criterion of analgesia is a 100% increase in response time over control. Established clinically active analgesics, such as "Demerol," (registered Trade Mark), codeine, etc., are active in the above test.

When mixed with suitable excipients or diluents the N-substituted anilides of the present invention can be prepared as pills, capsules, tablets or powders, for unit dosage and to simplify administration. As analgesics they will relieve pain by direct action on nerve centers or by diminishing the conductivity of the sensory nerve fibers.

The following Examples are illustrative of the general methods of preparing the compounds listed in the table. All the parts enumerated in the Examples are parts by weight.

EXAMPLE 1.

A mixture of 9.9 parts of N-(meta-chlorophenyl)-N^1,N^1-dimethylethylenediamine and 25 parts by volume of propionic anhydride is heated on the steam bath for three hours and then distilled. The portion which distills at 140°—144° C. (2.5 mm.) is N-(2-dimethylaminoethyl) - *meta* - chloro - propionanilide. The yield is 52%.

The hydrochloride salt is prepared by the addition of alcoholic hydrogen chloride to the ether solution of the base. The hydrochloride melts at 125°—127° C.

EXAMPLE 2.

A solution of 6.0 parts of N-(2-dimethylamino - 1 - methylethyl) - *meta* - hydroxyaniline in 25 parts by volume of alcohol is stirred, while 2.65 parts of propionyl chloride is added. The reaction mixture is left at room temperature for 16 hours and is then refluxed for 2 hours. It is concentrated, treated with 30 parts of 1N sodium hydroxide and extracted with ether. The ether layer is dried over magnesium sulfate and then distilled. N-(2 - dimethylamino - 1 - methylethyl) - *meta*-hydroxy-propionanilide distills at 170°—190° C. (0.8 mm.).

EXAMPLE 3.

A mixture of 8.2 parts of N,N-dimethyl-N^1-phenylethylenediamine and 20 parts of butyric anhydride is heated on the steam bath for three hours and then distilled. Pure N-(2-dimethylaminoethyl)-butyranilide is collected at 110°—115° C. (0.25 mm.). The yield is 50%.

A solution of 3.6 parts of the above oil in 9.6 parts by volume of 1.53 alcoholic HCl is diluted with ether and cooled. A precipitate separates and is filtered, washed with ether, and dried. The yield of N-(2-dimethylaminoethyl)-butyranilide hydrochloride, melting point 132°—133° C., is 72%.

EXAMPLE 4.

A mixture of 8.9 parts of N,N-dimethyl-N^1-(*p*-tolyl)-ethylenediamine and 20 parts of *iso*-butyric anhydride is heated on the steam bath for 17 hours and then distilled. The portion which boils at 112°—115° C. (0.1 mm.) is N-(2 - dimethylaminoethyl) - *p* - methyl - *iso*-butyranilide. The yield is 77%.

A solution of 7.9 g. of the above product in 20 parts by volume of 1.53 N alcoholic HCl is diluted with ether and then cooled. The precipitate of N-(2-dimethylaminoethyl)-*p*-methyl*iso*butyranilide hydrochloride is filtered washed with ether, and dried, melting point 179°—180° C.

EXAMPLE 5.

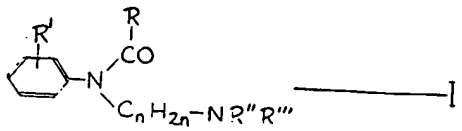
A mixture of 9.6 parts of N,N-diethyl-N^1-phenylethylenediamine and 25 parts by volume of valeric anhydride is heated on the steam bath for three hours and then distilled. The portion which boils at 142°—146° C. (1.5 mm.) is N-(2-diethylaminoethyl)-valeranilide.

EXAMPLE 6.

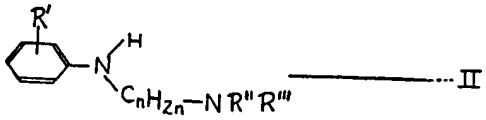
A mixture of 2.6 parts of N-(2-morpholinoethyl)-propionalide and 1.8 parts by volume of 5.25 N nitric acid is concentrated to dryness and then triturated with ether. The crystals are filtered and then recrystallized from ethanol. The pure N-(2-morpholinoethyl)-propionanilide nitrate melts at 143°—144° C.

WHAT WE CLAIM IS:—

1. A process of preparing N-substituted anilides having the general formula:



in which R is an alkyl group containing 1 to 4 carbon atoms, R^1 is hydrogen, halogen, dihalogen, hydroxyl, or an alkyl, alkoxy, alkanoyloxy, or an alkanoylamino radical each containing not more than six carbon atoms, R^{11} and R^{111} are alkyl radicals each containing not more than six carbon atoms or when taken together with the nitrogen atom to which they are attached form the residue of a saturated heterocyclic amine and n is 2 or 3, which process comprises reacting an N-substituted aniline having the formula:



in which R^1, R^{11}, $R^{11\,1}$, and n are as defined above, with an acylating agent containing the group RCO, in which R is as defined above.

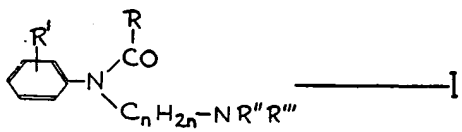
2. A process according to claim 1, in which said acylating agent is an acyl anhydride or acyl halide.

3. A process according to claims 1 or 2, in which the reactants are heated on a steam bath, the desired product then being distilled off.

4. A process of preparing N-substituted anilides having the general formula I substantially as hereinbefore described.

5. N-substituted anilides having the general formula I whenever prepared by the process according to any of the preceding claims.

6. N-Substituted anilides having the general formula:—



and acid addition salts thereof in which R is an alkyl group containing 1 to 4 carbon atoms, R^1 is hydrogen, halogen, dihalogen, hydroxyl, or an alkyl, alkoxy, alkanoyloxy, or an alkanoylamino radical each containing not more than six carbon atoms, R^{11} and R^{111} are alkyl radicals each containing not more than six carbon atoms, or when taken together with the nitrogen atom to which they are attached form the residue of a saturated heterocyclic amine and n is 2 or 3.

7. N-(1-methyl-2-piperidinoethyl)-propionanilide and acid addition salts thereof.

8. N-(2-piperidinopropyl)-propionanilide and acid addition salts thereof.

9. N-(2-diethylaminoethyl)-*meta*-chloropropionanilide and acid addition salts thereof.

10. N-(2-dimethylaminoethyl)-*para*-methyl-*iso*butyranilide and acid addition salts thereof.

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